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### **REMARKS**

Claims 9-23 are pending as of the mailing date of the Final Office Action. The specification has been amended at paragraph [0056] to remove alleged new matter in accordance with the Examiner's requirement. Independent claim 10 has been canceled. New claim 24 has been added that corresponds to canceled claim 10, amended to recite that the method is carried out *in vitro* and removing reference to the method being carried out in an organism. Claims 9 and 23 have been amended to recite that the method is performed *in vitro*. Support for the amendments to the claims can be found in the specification and claims as filed. The amendments add no new matter. Applicant submits that the amendments place the application in condition for allowance, and Applicant respectfully requests entry of the amendments.

### **Objection to the Specification**

The Examiner objected to the specification as allegedly being amended to include new matter and required that Applicant cancel the alleged new matter. The Examiner asserted that amendment of the specification at paragraph [0056] to recite specific columns and lines of a patent that was incorporated by reference as of the filing date of this application represented an amendment introducing new matter into the specification.

Applicant herein amends the specification to remove the alleged new matter in order to expedite prosecution.

### **Claim Objections**

The Examiner objected to the claims on the basis that a claim that depends from a dependent claim should not be separated by any claim that does not also depend on the dependent claim. The Examiner indicated that claims 11-22 are separated from claim 9 by independent claim 10.

Applicant has canceled claim 10 and added new claim 24, corresponding to claim 10,

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to address the Examiner's objection. Accordingly, no independent claim now separates claims 9 and 11-22.

**Rejections Under 35 U.S.C. § 112, First Paragraph: Written Description**

The Examiner rejected claims 9-23 as allegedly failing to satisfy the written description requirement, asserting that the disclosure fails to provide an adequate written description of how the claimed methods are to be performed. The Examiner asserted that none of the examples in the specification are drawn to the claimed methods, indicating that the claims include performing the methods *in vivo*, and asserting that introducing RNA having the structure  $X_1-L-X_2$  into any cell and having such transfection result in the desired end product is most difficult and unpredictable.

The Examiner also asserted that the ability to selectively and effectively target the correct target gene is critical, and that the specification is essentially silent as to what the target genes are and how to identify a suitable gene as compared to an unsuitable gene. Further, the Examiner asserted that the specification does not disclose how to perform the methods for any and all life forms, including humans.

Applicant herein amends the claims to recite that the method is carried out *in vitro*, and to remove reference to performing the claimed methods in an organism. Applicant submits that the amendments overcome the Examiner's written description rejections regarding *in vivo* application of the claimed methods. The Examiner's remaining objections are addressed below.

Applicant refers the Examiner to arguments previously made of record in Applicant's response filed 27 September 2004, and Applicant respectfully disagrees with the Examiner's written description rejections. The written description requirement is satisfied when an application describes the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath*,

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*Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). But the disclosure as originally filed does not need to provide *in haec verba* support for the claimed subject matter at issue. *Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320 (Fed Cir. 2000) (citation omitted). Rather, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question. *Fujikawa v. Wattanasin*, 93 F.3d 1559 (Fed. Cir. 1996). If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the written description requirement is met; the Examiner's burden is to provide reasons why a person of ordinary skill in the art would not consider the description sufficient. *In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996).

Applicant submits that the Examiner has not established why a person of ordinary skill in the art would not consider the description sufficient with regard to introducing, *in vitro*, an RNA having the structure X<sub>1</sub>-L-X<sub>2</sub> into a cell other than the cells disclosed in the specification, and having the transfection result in inhibition of an RNA. No reason has been articulated as to why a person of ordinary skill in the art would doubt that RNA comprising the structure X<sub>1</sub>-L-X<sub>2</sub> could be transfected into any cell type known in the art that is capable of being transfected *in vitro* with a nucleic acid. Transfecting cells with nucleic acids was well known in the art at the time of filing. Accordingly, any alleged failure to describe transfection conditions in detail should not support a written description rejection.

Further, Applicant has adequately described how the A549 cells used to illustrate the claimed methods were transfected. See, for example, the specification as filed at page 14, second full paragraph. Examples of other disclosures of transfecting cells with nucleic acids are provided below.

Yu *et al.* (2002) *PNAS* 99/9:6047-6052 (Yu), cited previously against the claims by the Examiner, discloses transfection into mouse P19 cells (see, for example, Yu at page 6047,

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column 2, lines 8-10) of vectors coding for hairpin RNAs. Further, Yu indicates that transfection was performed by a method known in the art (see, for example, Yu at page 6048, paragraph straddling columns 1 and 2). Piccin *et al.* (2001) *Nucleic Acids Res.* 29/12 e55:1-5 (Piccin), submitted herewith in an information disclosure statement, also discloses introducing a transgene encoding for a hairpin RNA into *Drosophila melanogaster* P19 cells (see, for example, Piccin at page 2, col. 1, first sentence of first full paragraph, and page 1443, col. 2, final paragraph). These references establish that introducing nucleic acids into cells, in particular for performing RNA interference, was well known in the art before the priority date of the instant application. Accordingly, Applicant submits that a person of ordinary skill would have understood the inventor to have been in possession of the claimed invention at the time of filing.

Applicant also respectfully disagrees that the written description requirement is not met because the application allegedly does not disclose how to identify a target gene or suitable gene and how to selectively and effectively target the gene. Methods for selecting hairpin RNA that are capable of inhibiting a target mRNA were known in the art at the time the application was filed. Examples of disclosures published before the priority date of the instant application that describe how hairpin RNAs are selected with respect to their targets are provided below. In light of these references, a person of ordinary skill in the art would readily appreciate that the inventors were in possession of the claimed invention at the time the application was filed.

Yu discloses that hairpin siRNAs can effectively inhibit RNAs that are complementary to either the sense or antisense siRNAs (see, for example, Yu at page 6049, col. 2, final paragraph) to achieve RNA interference. The Examiner is also referred to Piccin, which also shows transfection of a construct that gives rise to a hairpin RNA effective in performing RNA interference. Piccin discloses that "[i]ntroduction of double-stranded RNA (dsRNA) triggers degradation of the mRNA bearing the same sequence in a variety of organisms," and discloses a transgene that gives rise to a hairpin siRNA within a cell

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following transfection. Yu and Piccin establish that it was known in the art before the filing date that RNA sequences in hairpin RNAs, such as those designated X<sub>1</sub> and X<sub>2</sub> of the present claims, can be selected by making X<sub>1</sub> or X<sub>2</sub> complementary to the mRNA to be inhibited. Accordingly, the written description requirement is satisfied and no reasonable basis exists to doubt that a person of ordinary skill in the art would find the disclosure sufficient.

**Rejections Under 35 U.S.C. § 112, First Paragraph: Enablement**

The Examiner rejected claims 9-23 as allegedly failing to comply with the enablement requirement. The Examiner asserted that none of the intended utilities have been fully enabled by the specification, including gene therapy or identification of a gene as a suitable target for drug development. The Examiner also asserted that the specification does not include the requisite starting materials and reaction conditions that would permit a person of ordinary skill in the art to reproducibly manufacture any and all useful interfering hairpin RNA molecules, asserting that the methods of claims 9 and 11-23 encompass gene therapy in any individual, including a human. Further, the Examiner asserted that the specification is silent as to what mRNA sequences are to be used and how they are to be introduced into any subject to selectively diminish mRNA transcription without resulting in toxicity to a cell/individual.

Applicant has amended the claims to recite that the method is carried out *in vitro*. Reference to using the method in an organism in claim 10 has been addressed by canceling claim 10 and adding new claim 24, which omits reference to carrying out the method in an organism. Applicant submits that the amendments to the claims overcome the Examiner's enablement rejections, and Applicant addresses the Examiner's rejections in relation to the amended claims below to the extent that the Examiner may apply the rejections to the amended claims.

The Examiner is referred to arguments in support of the claims previously made of record in Applicant's response of 27 September 2004. The Examiner is also referred to

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arguments made above in connection with Applicant's response to the Examiner's written description rejections.

To satisfy the enablement requirement, the claimed invention must be enabled so that a person of skill in the art could make and use the invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The test is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art, without undue experimentation. *U.S. v. Teletronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). In determining whether the enablement requirement is satisfied, it is to be noted that a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). To state a *prima facie* enablement rejection, an Examiner must establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1999).

Applicant submits that the Examiner has not provided a reasonable basis to doubt the objective truth of the statements in the specification that teach how carry out the methods of the amended claims. In particular, Applicant submits that no reasonable basis is articulated to doubt the objective truth of the teaching contained in page 8, line 26 to page 9, line 34; page 12, line 21 to page 13, line 27; and page 14, line 22 to page 15, line 13 as to making the exemplary RNAs, and paragraphs page 10, lines 1 to 27; page 14, lines 4 to 18; and page 15, lines 2-13 as to using the exemplary RNAs, and the Figures. Thus, the specification fully enables methods for inhibiting a target mRNA *in vitro* in accordance with the amended claims.

Further, Applicant submits that new claim 24, corresponding to canceled claim 10, is enabled. Claim 24 recites that the method is carried out *in vitro*, and omits reference to carrying out the method in an organism. Accordingly, new claim 24 includes assaying *in*

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*vitro* whether a gene product is a suitable target for drug discovery. Applicant refers the Examiner to the arguments made above regarding selection of  $X_1$  and  $X_2$  sequences directed against a target gene. Applicant submits that the method of new claim 24 can be employed using a hairpin RNA against any coding region of a genome. If inhibiting the mRNA of a target gene results in an effect in the cell, that is, results in a measurable phenotype, then the product of the target gene can be a target for drug discovery, wherein drug discovery is aimed at producing the same measurable phenotype. See, for example, page 10, lines 12-19 of the application as filed.

Additionally, Applicant respectfully disagrees with the Examiner's arguments that this case is analogous to *Genentech v. Novo Nordisk* ("*Genentech*"). *Genentech* was decided on strikingly different facts. In *Genentech*, the claims recited a method for making human growth hormone in a fusion protein and cleaving the fusion protein to make the growth hormone. The patentees in *Genentech* tried to rely on the level of skill in the art to enable the claim, but at the time of filing the application it was *not* known in the art how to cleave a fusion protein to make growth hormone, *where the cleaving of the fusion protein was the novel aspect of the claim*. In contrast, the novel aspect of the amended claims does not include novel methods for selecting nucleotide sequences against target mRNAs. As set forth above in Applicant's remarks regarding the written description rejections, methods of selecting sequences for hairpin RNAs that are at least active against a target mRNA were known in the art at the time the instant application was filed. Accordingly, Applicant submits that an enablement rejection of the amended claims predicated on an alleged lack of a discussion of how to select an RNA sequence for a hairpin RNA that is at least active against a target mRNA would be improper.

Accordingly, in light of the amendments and remarks above, Applicant requests reconsideration and withdrawal of the written description and enablement rejections.

### Conclusion

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In view of the foregoing, reconsideration and allowance are respectfully solicited.

No fee is believed to be due with respect to the filing of this amendment. If any fees are due, or an overpayment has been made, please charge, or credit, Deposit Account No. 11-0171 for such sum.

If the Examiner has any questions regarding the present application, the Examiner is cordially invited to contact Applicant's attorney at the telephone number provided below.

Respectfully submitted,



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